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Immunity-targeted approaches to the management of chronic and recurrent upper respiratory tract disorders in children

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Background: Upper respiratory tract infections (URTIs), including rhinitis, nasopharyngitis, tonsillitis and otitis media (OM), comprise of 88% of total respiratory infections, especially in children. Therefore effective prevention and treatment of RTIs remain a high priority worldwide. Preclinical and clinical data highlight the rationale for the use and effectiveness of immunity-targeted approaches, including targeted immunisations and non-specific immunomodulation in the prevention and management of recurrent upper RTIs.

Objective of review: The idea of this review was to summarise the current evidence and address key questions concerning the use of conservative and immunity-targeted approaches to recurrent and chronic URTIs, with a focus on the paediatric population.

Search strategy/Evaluation method: Literature searches were conducted in March 2017 and updated in September 2017 using: Academic Search Complete; CENTRAL; Health Source: Nursing/Academic Edition; MEDLINE; clinicaltrials.gov; and Cochrane databases. In total, 84 articles were retrieved and reviewed. Two independent researchers focused on primary and secondary endpoints in systematic reviews, meta-analyses and randomised, controlled trials, using immunity-directed strategies as the control group or within a subpopulation of larger studies. Existing guidelines and interventional/observational studies on novel applications were also included.

Results: Children are particularly susceptible to RTIs due to the relative immaturity of their immune systems, as well as other potential predisposing factors such as day care attendance and/or toxic environmental factors (eg increased pathogenic microbial exposure and air pollutants). Recurrent URTIs can affect otherwise healthy children, leading to clinical sequelae and complications, including the development of chronic conditions or the need for surgery. Available pre-clinical and clinical data highlight the rationale for the use and effectiveness of immunity-targeted approaches, including targeted immunisations (flu and pneumococcal vaccines) and non-specific immunomodulation (bacterial lysates), in the prevention and management of recurrent croup, tonsillitis, otitis media, recurrent acute rhinosinusitis and chronic rhinosinusitis.

Conclusions: In this review, we summarise the current evidence and provide data demonstrating that some immunity-targeted strategies, including vaccination and immunomodulation, have proved effective in the treatment and prevention of recurrent and chronic URTIs in children.

1 | RESPIRATORY TRACT INFECTIONS

1.1 | Introduction

Upper respiratory tract infections (URTIs; also known as ENT infections), including rhinitis, nasopharyngitis, tonsillitis and otitis media (OM), comprise 88% of total respiratory infections.¹ The aetiology of URTIs is mostly viral, being primarily caused by rhinovirus (HRV), parainfluenza, respiratory syncytial virus (RSV), influenza, adenovirus and coronavirus. Upper respiratory tract infections are more common in the autumn/winter in Europe and North America, and during the rainy season in tropical countries.²

Children are prone to developing RTIs because their immune system has yet to fully mature.³⁻⁵ Increased exposure to viral infections during day care attendance, as well as other social and environmental factors, can increase the risk of RTI.⁴ The respiratory system is a primary target for key air pollutants, which can increase the risk of acute and recurrent RTIs.⁶ Most of these pollutants disrupt local mucosal innate immunity mechanisms, leading to bacterial colonisation, impaired killing and increased allergen permeability.

1.2 | Burden and management of RTIs

URTIs are associated with sequelae and complications, including severe lower RTIs (LRTIs), the development of chronic conditions or the need for surgery when recurrent. Owing to the high morbidity, mortality and healthcare costs, effective prevention and treatment of RTIs are a high priority worldwide.^{7,8} Treatment is focused on symptom relief, such as antihistamines and decongestants for nasal congestion⁹ and antitussives for cough.^{10,11} Although antibiotics are only indicated in a minority of patients, they are often unnecessarily prescribed for viral infections against which they have no effect. A recent US report highlighted that ~30% of outpatient, oral antibiotic prescriptions were inappropriately written.¹² Antibiotic misuse has led to the emergence of resistant bacteria, meaning that higher doses and more advanced generations of drugs are required, and at present, some infected patients cannot be treated adequately.¹³

Owing to the current unmet need for effective, alternative conservative therapies, efforts are being refocused towards preventative strategies including⁵ behavioural intervention; avoidance of environmental risk factors such as passive smoking¹⁴ and highly polluted city areas; vaccination, such as active targeted immunisation; targeted medical intervention; non-specific immunostimulation or immunomodulation (eg bacterial lysates)¹⁵⁻¹⁸; nutrition, including vitamins (eg C or D) and microelements; and regular physical activity

Key points

- Upper RTIs comprise 88% of total respiratory infections
- Children are particularly susceptible to RTIs because their immune system has yet to fully mature
- Recurrent URTIs can affect otherwise healthy children, leading to clinical sequelae and complications
- Owing to the high morbidity, mortality and healthcare costs, effective prevention and treatment of RTIs are a high priority worldwide
- Pre-clinical and clinical data highlight the rationale for the use and effectiveness of immunity-targeted approaches, including targeted immunisations and non-specific immunomodulation in the prevention and management of recurrent upper RTIs.

(Table 1). Parents of children with recurrent RTIs may also discuss “immune-stimulating” therapies that they have seen advertised, such as herbal (eg Echinacea) and homoeopathic remedies, and animal-derived products (eg cod liver oil and thymus extracts).⁵ Owing to significant heterogeneity and a lack of high-quality clinical evidence supporting many of these therapies,¹⁹ here we reviewed existing immunity-targeted therapies available for ENT infections in children, with an emphasis on non-specific immunomodulation administered together with the standard of care.

1.3 | Role of immunomodulation in respiratory tract infections

Immunomodulatory strategies treat RTIs by enhancing local and systemic immune responses. Systemic effects relate to the use of microbial-derived preparations (bacterial lysates, bacterial ribosomes) that display effects such as increased systemic polyclonal immunoglobulin (Ig) synthesis (both IgA and IgG classes) and activation of several populations of immunocompetent cells (including CD4+ lymphocytes, natural killer cells, and B lymphocytes).²⁰ These effects have consequently been reported in both in vitro and in vivo experiments (for review, see Kearney et al).²¹

A number of clinical studies have shown that bacterial lysates and bacterial organelles (eg ribosomes), when applied orally, are effective in preventing both URTI and LRTIs in children, decreasing the number, duration and severity of infectious episodes,

TABLE 1 Current preventative and evidence-based immunity-targeted approaches in the management of recurrent URTIs

Environmental	Behavioural	Nutritional	Systemic
<ul style="list-style-type: none"> • Protection from noxious environmental factors (passive smoking, traffic-related pollution) 	<ul style="list-style-type: none"> • Improved hand washing • Increased physical activity • Avoiding crowded communities 	<ul style="list-style-type: none"> • Zinc • Vitamin D 	<ul style="list-style-type: none"> • Immunisation • Oral immunostimulators/Immunomodulators, for example bacterial lysates, herbal products, probiotics, other chemical compounds

URTI, upper respiratory tract infection.

reducing antibacterial use and decreasing the number of work/school absences.^{22,23} Immunomodulation with bacterial lysates is of particular interest because several randomised, controlled trials, summarised in systematic reviews or meta-analyses, have demonstrated their efficacy in children with RTIs.^{19,24,25} A plausible mechanism of action for bacterial lysates has been proposed, which is not only based on an increase in non-specific immunoglobulin A response against pathogens at mucosal surfaces, but also on activation of mucosal dendritic cells by pattern recognition receptor-dependent signalling.²⁶ They act on both innate and adaptive immune responses, with recent findings supporting antiviral effects (eg increased interferon [IFN]- γ , IFN- α and IFN- β).²⁶⁻²⁸ Interestingly, application of bacterial lysates also produces systemic effects, including increased serum immunoglobulin concentrations²⁹ and systemic CD4+ T-helper cell responses to bacterial antigens. For a comprehensive review of the mechanism of action of bacterial lysates, see Kearney et al 2015 and Esposito et al 2018.^{21,30} Immunomodulation with bacterial lysates has been empirically well accepted and used by the medical community for decades for treating RTIs,¹⁹ and one of these commercially available compounds (OM-85) has been incorporated into various clinical treatment guidelines such as those from the Pan American Association of Otorhinolaryngology and Head and Neck Surgery³¹ and a European Position (EPOS) paper³² (albeit only for the management of specific chronic respiratory conditions in adults, as studies in children were not comprehensively evaluated) with the highest recommendation grade. More recently, OM-85 has been recommended for the prevention of RTIs in children in several international guidelines.^{33,34} Systemic strategies include the application of medications or dietary factors that may enhance systemic immune responses, such as zinc preparation intake, vitamin D supplementation and probiotics; however, their clinical effectiveness remains debatable.

In this review, we want to highlight emerging, evidence-based approaches for conservative management of the most common recurrent and chronic URTIs in children, with an emphasis on the role of immunomodulation.

2 | METHODOLOGY

2.1 | Search strategy and evaluation method

Literature searches were initially conducted in March 2017 and then updated in September 2017 using: Academic Search Complete; CENTRAL; Health Source: Nursing/Academic Edition; MEDLINE; clinicaltrials.gov; and Cochrane databases. In total, 84 articles were retrieved and reviewed. Two independent researchers focused on the primary and secondary endpoints reported in systematic reviews, meta-analyses and randomised, controlled trials, using immunity-directed strategies as the control group or within a subpopulation of larger studies. Existing guidelines and interventional or observational studies on novel applications were also included in the literature searches.

2.2 | Ethical considerations

As no human participants were involved in the development of this review, no ethics committee (Institutional Review Board) approval was sought or obtained, and it was not necessary to obtain informed consent from patients.

3 | CROUP

3.1 | Introduction

Children with recurrent or severe croup are commonly referred to a paediatric otolaryngologist or ENT specialist for further assessment and exclusion of an underlying anatomical or congenital upper airway disorder.

3.2 | Epidemiology

Croup occurs at a rate of ~5/100 in the second year of life, with a peak incidence between 6 months and 3 years of age.³⁵ Around 15% of annual clinic and emergency department visits for paediatric RTIs are due to croup.³⁵ Recurrent croup in children is typically defined as more than three episodes.³⁶

3.3 | Aetiology

Croup is primarily caused by parainfluenza viruses 1, 2 and 3, as well as RSVs. The viruses are generally spread by direct inhalation from a cough or sneeze, or by contamination of the hands following contact with fomites, with subsequent transference to the mucosa of the eyes, nose or mouth.

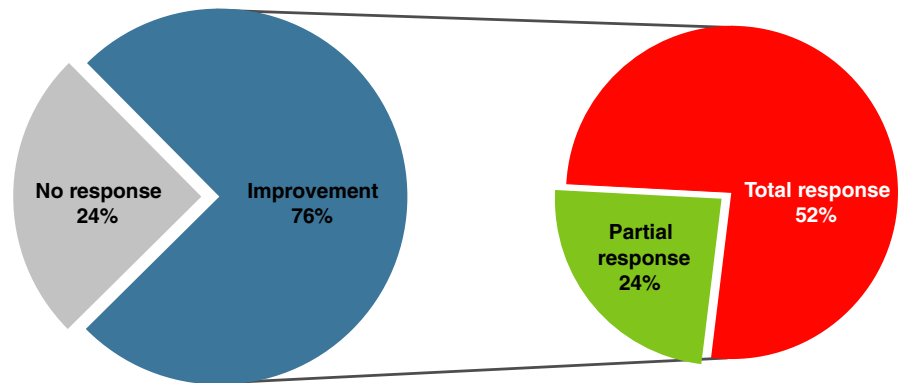
3.4 | Treatment of acute or recurrent episodes

The treatment of croup is dependent on the severity of the upper airway obstruction and the risk for rapid deterioration of the patient's condition. Mild-to-moderate croup is typically treated with anti-inflammatory agents (nebulised or oral steroids), while adrenaline is required urgently in cases of severe croup.³⁷ The use of systemic corticosteroids early in the disease process reduces hospitalisation rates,³⁸ although 6-10% of patients still require hospitalisation.³⁹

3.5 | Prevention of recurrent episodes and the role of immunomodulation

Several evidence-based treatment guidelines for croup are currently available online, including those from the UK,⁴⁰ Australia,⁴¹ Poland⁴² and Finland.⁴³ However, these guidelines provide only general measures for lowering the risk of respiratory infections. There are currently no vaccines targeting the viruses responsible for croup, despite a number of attempts to develop them.⁴⁴⁻⁴⁶ Achieving satisfactory immunogenicity has proved challenging,^{47,48} although ongoing clinical trials (see clinicaltrials.

FIGURE 1 Bacterial-derived immunomodulator in the prevention of acute tonsillitis (Reprinted from Bitar & Saade, Copyright © 2013, with permission from Elsevier).⁵⁷ "Total response" was defined as a >50% decrease in acute tonsillitis episodes at the end of treatment (ie 6 months); "partial response" was defined as a ≤50% decrease in acute tonsillitis episodes at the end of treatment. The immunomodulator used was OM-85



gov: NCT00186927) are assessing new, well-tolerated vaccines. Since most croup-causing viruses also cause URTIs, there could be a therapeutic role for other immunomodulatory strategies, although well-defined, controlled studies are required.

4 | RECURRENT TONSILLITIS

4.1 | Epidemiology

Tonsillitis is more common among children than adults.^{49,50} In the USA, sore throat accounts for 2.1% of outpatient visits,⁵¹ with a prevalence of bacterial tonsillitis of 15–30% among affected children.^{52–54} Recurrent tonsillitis in children is defined as multiple episodes of acute tonsillitis in a year.⁵⁵ The burden of recurrent tonsillitis is substantial and it may lead to peritonsillitis. However, the overall frequency and magnitude of the problem of recurrent tonsillitis remains unclear.

4.2 | Treatment of acute and recurrent episodes

The treatment of tonsillitis in children focuses on reducing symptoms, avoiding complications, decreasing the number of disease-related school absences and improving quality of life. According to clinical practice guidelines, the first-line treatment for bacterial tonsillitis should be a narrow-spectrum antibiotic (eg penicillin).^{16,49,50} However, some European countries, including Germany, the UK and the Netherlands, only recommend antibiotics in certain high-risk patients.⁵⁶ The widely accepted indications for tonsillectomy in children are at least seven well-documented, clinically significant, adequately treated sore throat (defined as "acute pharyngitis, tonsillitis or acute exudative tonsillitis") in the preceding year, or at least five such episodes in each of the preceding 2 years, or at least three such episodes in each of the preceding 3 years.^{49,50} Surgery should also be considered if the episodes are disabling and prevent normal functioning.

4.3 | Prevention of recurrent episodes and role of immunomodulation

Microbial-derived preparations seem to offer an attractive alternative approach in prevention of tonsillitis. Firstly, in a retrospective,

observational study of 131 children aged 1–15 years with recurrent acute tonsillitis, 76% treated with a commercially available bacterial lysate (OM-85) had a decrease in the frequency of acute tonsillitis episodes after 6 months (Figure 1).⁵⁷ Most (67%) had a greater than 50% decrease in the number of episodes, and none required a tonsillectomy in the subsequent long-term follow-up period. Secondly, in a 90-day trial with the oral probiotic *Streptococcus salivarius* K12, all 30 children who completed the study had a significant reduction in streptococcal pharyngeal infection episodes (more than 90%) compared with the previous year, as well as a significant decrease in the incidence (80%) of oral viral infections⁵⁸; no difference was observed in the control group. Similar results were observed in an earlier study.⁵⁹ Finally, in a study of 160 children aged 5–14 years with pharyngotonsillitis, ribosomal immunotherapy led to a significant improvement in both specific immunity and non-specific immunity and may therefore be effective in the prophylaxis of recurrent pharyngotonsillitis.⁶⁰

5 | OTITIS MEDIA

5.1 | Epidemiology

Acute OM (AOM) is a viral or bacterial infection of the middle ear and is the most common childhood infection for which antibiotics are prescribed in the USA.^{12,61} Recurrent AOM is typically defined as at least three episodes in a 6-month period, or four or more episodes in a 12-month period including at least one episode in the preceding 6 months.⁶² There are a number of risk factors for AOM recurrence, including the winter season, male gender and passive smoking.⁶² Approximately 50% of children aged less than 2 years treated for AOM experience a recurrence within 6 months.⁶² Symptoms that last for more than 10 days may also predict recurrence.⁶³

5.2 | Treatment of acute and recurrent episodes

The treatment approach in AOM depends on factors such as patient age and the severity of signs and symptoms.⁶² Non-invasive treatment interventions include no treatment/ watchful waiting (but predisposing conditions such as immunodeficiency, anatomic

malformations, cystic fibrosis and ciliary dyskinesia need to be excluded); greater patient/parent education, such as highlighting the importance of avoiding passive smoking, as this is a significant factor impairing mucosal immunity; and breastfeeding for children aged less than 1 year.⁶⁴ More invasive interventions, such as the insertion of tympanostomy tubes, may be required for children with recurrent AOM and one or more of the following: aged less than 2 years; underlying medical conditions that predispose the patient to recurrence; or comorbid conditions associated with developmental or language delays. However, there is generally a lack of consensus regarding the role of surgery in AOM.⁶⁵ The parents of children with recurrent AOM are usually anxious about pursuing a surgical treatment option and often seek complementary remedies.⁶⁶

5.3 | Prevention of recurrent episodes and role of immunomodulation

A key recommendation from the guidelines of the American Academy of Pediatrics (AAP) is that "clinicians should NOT prescribe prophylactic antibiotics to reduce the frequency of episodes of AOM in children with recurrent AOM."⁶² Pneumococcal and influenza vaccines, given according to the schedule recommended in the AAP guidelines, are recommended.⁶² Indeed, a recent analysis found that the epidemiology of AOM has changed substantially over the past 30 years, highlighted by a decrease in the number of AOM episodes and the number of otitis-prone children. The authors concluded that this epidemiological shift is associated with the introduction of pneumococcal conjugate vaccines (PCVs) and also due to the development of more stringent diagnostic criteria.⁶⁷ Stopping smoking and banning smoking in public places significantly decreased the rate of children's emergency department visits for middle ear infections and URTIs by 6-9%, according to a study from Massachusetts, USA.⁶⁸ Probiotics have been shown to be ineffective in patients with AOM.⁶⁹ There may be a role for the use of vitamin D, since levels have been shown to be significantly lower in children with AOM compared with controls.^{70,71} There is also evidence that the incidence of AOM in children can be reduced using immunity-targeted microbial preparations. For example, the frequency of AOM was assessed as a secondary endpoint in two clinical studies of the bacterial lysate OM-85 involving children with recurrent acute RTIs. Bacterial lysate treatment reduced the total number of OM episodes by 68% at 6 months ($n = 25$ vs 8 , respectively)⁷² and by 79% at 12 months ($n = 14$ vs 3 , respectively)⁷³ compared with placebo. Of note, a randomised controlled Italian study of OM-85 for the prevention of URTIs (with AOM as a study outcome) in children with risk factors for URTIs and a history of recurrence is planned (EudraCT: 2016-002705-19). Ribosomal bacterial immunotherapy has also demonstrated efficacy in children with AOM. In a study of 84 patients aged 4-14 years, ribosomal immunotherapy led to a significantly improved outcome versus placebo on the incidence of fever, as well as the frequency and duration of infectious episodes.⁷⁴ Ribosomal immunotherapy

led to significant improvements in clinical score, immunological parameters, parents' assessment of the patient's symptoms and hearing tests, compared with placebo, in a study of 72 patients aged 6-14 years.⁷⁵ In addition, a meta-analysis of 19 randomised, double-blind studies, including 1215 children, demonstrated a significantly lower need for surgical procedures with ribosomal immunotherapy (1% vs 7% with placebo) in patients with recurrent AOM.⁷⁶

6 | RECURRENT ACUTE AND CHRONIC RHINOSINUSITIS

6.1 | Epidemiology

The EPOS group defined acute rhinosinusitis (ARS) as "the sudden onset of two or more symptoms that last for <12 weeks."³² However, in older classifications the term "subacute sinusitis" was proposed, which represents a temporal progression of symptoms for 4-12 weeks (contemporarily defined as "post-viral ARS"). Although chronic rhinosinusitis (CRS) is defined as persistence of sinus inflammation for at least 12 weeks, the EPOS group did not feel a separate term to describe patients with prolonged ARS was necessary, and that "exacerbation of CRS" was more appropriate. In Europe, 0.5-5% of children with URTIs progress to post-viral ARS^{77,78} and many experience recurrences (point prevalence of 0.035%).⁷⁹ Estimates of CRS prevalence vary significantly worldwide, partly related to differences in the diagnostic criteria used (eg symptom-based diagnosis vs inclusion of objective rhinoscopy or imaging findings). In the USA, the prevalence of CRS ranges from 2% to 16%, while in various EU countries, it is 7-27% (average 11%).⁷⁷ Estimates from South America and the Caribbean are in a similar range.^{80,81}

Differentiation between recurrent ARS and CRS is difficult, but relies on the complete resolution of symptoms between episodes.⁸² Some patients have recurrent episodes of ARS and may represent a distinct clinical phenotype⁸³; these patients should be assessed for underlying risk factors such as allergy, immunodeficiency, cystic fibrosis and anatomical abnormalities,⁸⁴ with consideration of imaging or endoscopic evaluation. As the nasal/paranasal mucosa is the first interface with inhaled toxins and pollutants, environmental factors are thought to be an important cause of transition from ARS to CRS, as well as the trigger for symptom exacerbation in CRS.⁸⁵ For example, there is a significant association between passive smoking and sinusitis.⁸⁶

6.2 | Treatment of acute and recurrent episodes

Careful analysis of the underlying defect should be performed, for example anatomical abnormalities and immunodeficiency.^{87,88} The prophylactic treatment of recurrent episodes is almost the same as prevention of exacerbation of CRS, that is avoidance of smoking and air pollution, and handwashing to prevent infections. However, in our opinion, the treatment modalities for CRS in children proposed by the Pan American Association in 2011, the EPOS group in 2012

and an International Consensus Statement in 2016, need some refinement, since some important studies have only been published recently while others were overlooked. Firstly, according to a recent Cochrane meta-analysis evaluating intranasal steroids for CRS in children, there was no effect on disease severity, although symptomatic improvement (nasal blockage, rhinorrhoea, loss of sense of smell and facial pain) was observed.⁸⁹ Based on these observations, we recommend intranasal steroids as a category Ia/A option for children with recurrent ARS and/or CRS.⁸⁹ Secondly, in a randomised, double-blind study in 51 children, bacterial lysate OM-85 (recommended as a Ia/A option by EPOS for adults with CRS only, as studies in children were not comprehensively evaluated) not only improved CRS symptoms (nasal discharge and obstruction) and reduced the frequency of CRS exacerbations, but they also decreased the number of days with antibiotic use/month, providing long-term prophylaxis.⁹⁰ Moreover, this study found that the duration of acute episodes was shorter with bacterial lysates than placebo, suggesting an additional value as a co-medication for the treatment of CRS.⁹⁰ These observations were supported by two other randomised, double-blind studies in children (aged 1-9 years) with recurrent ARS,^{91,92} highlighting the clinical value of non-specific, immunomodulatory approaches. Table 2 summarises the evidence and recommendations for the management of children with recurrent ARS/exacerbations of CRS as proposed by EPOS, including our own modifications.³² A recent international consensus statement

also provided evidence-based recommendations for the treatment of rhinosinusitis.⁸²

6.3 | Prevention of recurrent episodes and role of immunomodulation

Immunisation leads to an increase in the host's resistance capabilities and a decrease in the incidence of acute respiratory disease.⁹³ Vaccination against pneumococci with the 7-valent pneumococcal vaccine (PCV7) resulted in a significant shift in the causative pathogens of acute maxillary sinusitis in children; the frequency of *Streptococcus pneumoniae* decreased by 18%, but the proportion of *Haemophilus influenzae* increased by 8%.⁹⁴ Although there is no strong evidence of a change in the incidence of acute bacterial rhinosinusitis after widespread use of PCV, the *H influenzae* type b vaccine has had a positive effect.⁹⁵ Another group of immune-active agents, bacterial-derived immunomodulators, has been shown to reduce the number of seasonal URTIs¹⁹ and decrease the frequency and intensity of ARS episodes or CRS exacerbations.⁹⁶ Based on evidence in adults with CRS without nasal polyps,⁹⁷ the EPOS paper and the Pan American Association of Otorhinolaryngology and Head and Neck Surgery guidelines recommend a bacterial lysate (OM-85), although only in adults.^{31,32} Nevertheless, there is substantial evidence supporting the value of bacterial lysates to reduce the risk for acute RTIs in children, as evidenced by a Cochrane review,¹⁹ a recent large meta-analysis of almost 5000 paediatric patients²⁵ and clinical studies highlighting the prevention of exacerbations of CRS or recurrent ARS.⁹⁰⁻⁹² Supported by these findings, several consensus papers and guidelines have noted that OM-85 could play a role in the prevention of recurrent rhinosinusitis in children.^{33,34,98}

Seasonal URTIs are the most common cause of recurrent ARS/exacerbation of CRS. In a Cochrane review evaluating zinc and the common cold, which included 18 randomised controlled trials and 1781 children and adults, it was concluded that zinc could shorten episode duration in children and also be used as a preventative measure⁹⁹; further research should focus on the effect of zinc in patients at a greater risk of developing complications after a common cold. A recent meta-analysis of 25 randomised controlled trials (including 11 321 children and adults) found that vitamin D supplementation significantly reduced the risk of acute RTIs, with the available evidence assessed as being high quality.¹⁰⁰ Although a large number of randomised controlled trials have been performed assessing Echinacea and the common cold,¹⁰¹ the weakness of trial methods and differences in interventions make it difficult to draw conclusions about its effectiveness in children. Similarly, despite a large number of studies and wide variety of available data, according to a systematic review, evidence supporting the use of vitamin C supplementation and the common cold is limited.¹⁰²

7 | DISCUSSION

7.1 | Summary of main findings

Although antimicrobials retain an important role in medicine, their use is becoming less acceptable in modern society, particularly for certain conditions or when administered as a preventative measure.

TABLE 2 Treatment options and recommendations for children with recurrent ARS/CRS exacerbations (adapted from EPOS,³² with our own modifications⁹⁰⁻⁹²)

Therapy	Level	Grade of recommendation
Nasal saline irrigation	Ia	A
Topical steroids	Ia	A
Bacterial lysates (OM-85)	Ib	A
PPI/GERD therapy	Low level evidence or no data	
Topical antimycotics	Low level evidence or no data	
Oral steroids	Low level evidence or no data	
Probiotics	Low level evidence or no data	
Short-term antibiotics (<4 wk)	Low level evidence or no data	
Intravenous antibiotics	Low level evidence or no data	
Oral long-term antibiotics	Low level evidence or no data	
Decongestants	Low level evidence or no data	
Mucolytics	Low level evidence or no data	
Oral/topical decongestants	Low level evidence or no data	
Allergen avoidance	Low level evidence or no data	
Allergen immunotherapy	Low level evidence or no data	
Systemic antimycotics	Low level evidence or no data	

Roman numerals indicate evidence levels; capital letters indicate recommendation grades. ARS, acute rhinosinusitis; CRS, chronic rhinosinusitis; EPOS, European Position; GERD, gastroesophageal reflux disease; PPI, proton-pump inhibitor.

The rapid emergence of resistant bacteria is jeopardising the efficacy of antibiotics; indeed, decreasing the use of antibiotics is considered a top priority for healthcare authorities around the world to avoid the consequent effects of overuse such as an increase in antibiotic resistance and mucosa microbiome impairment.¹⁰³ As such, new treatments and preventative modalities for respiratory infections are expected and welcomed. Modulation of the human immune systems is becoming increasingly relevant, not only in general infectious diseases, allergy or gastroenterology, but also in disciplines such as oncology and ENT-related disorders. In this review, we have discussed the clinical evidence that supports the use of selected immunomodulatory strategies in children with specific ENT conditions.

7.2 | Implications for clinical practice

However, there remain some barriers to the widespread use of these therapies. For example, the availability of data on specific ENT infections remain sparse, although evidence around the prevention of general RTIs is more robust. Ideally, new studies will be performed in specific ENT infections in children, in order to increase the evidence base and support treatment recommendations. In addition, according to the available meta-analysis, many of the commercially available products demonstrate a moderate effect.

7.3 | Future directions

As such, it is important that we generate high-quality research data on the use of immunomodulatory strategies in patients with specific URTIs and other upper respiratory tract diseases.

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CONFLICT OF INTEREST

WF has been a speaker for Sandoz, Vifor Pharma, Pierre Fabre and GSK. RM, ASV and KR declare no conflict of interest. JLMB has been a speaker for MSD, Carnot, Grünenthal and has participated as an advisor for MSD and Vifor Pharma.

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